Summary of Clinical Information on NDA 20-996 for the Dermatologic and Ophthalmologic Drugs Advisory Committee

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1. Introduction

1.1. Zinc Chloride and 8-Hydroxyquinoline

Zinc chloride is available for intravenous nutritional supplementation. It has also been used as a fixative for Mohs surgery in the treatment of skin cancer.

8-Hydroxyquinoline is used as a chelating agent for ^{111}Indium in nuclear medicine. There are also published reports of its use as an antimicrobial agent in wound healing and in diaper rash.

Neither the chelated compound, zinc oxinate, nor the combination of zinc chloride and 8-hydroxyquinoline has been marketed.

1.2. Dermex's Zinc Oxinate Ointment

Dermex's zinc oxinate ointment is a combination of zinc chloride and 8-hydroxyquinoline in plastibase. Dermex believes the active ingredient to be the chelated zinc oxinate, while not ruling out that the 8-hydroxyquinoline serves merely as a transport agent.

2. Issues in the Filing of NDA 20-996

2.1. Original Submission of NDA on 3/27/98

- Six indications were sought: Kaposi's sarcoma, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, genital warts and verruca warts.
- The submission did not contain clinical information in the proper format or with adequate content to allow substantive review.
- Information on IRB approval of clinical studies was not provided.

2.2. Refuse-to-file Action

The RTF Letter states: "The application contains neither pivotal efficacy studies per indication which are adequate and well-controlled nor appropriately designed dose ranging and topical safety studies."

2.3. Resubmission of 9/15/99 and Filing over Protest

The resubmission of 9/15/99 also did not contain information in the proper format or with adequate content to allow substantive review. Neither were the issues in the RTF Letter of 7/1/98 (adequate and well-controlled studies, dose-ranging and topical safety studies) addressed. Thus this submission was not fileable, because of 21 CFR 314.101(d)(2)(3) and (7):

§314.101 (d) FDA may refuse to file an application or may not consider an abbreviated new drug application to be received if any of the following applies:

(2) The application is not submitted in the form required under Sec. 314.50 or Sec. 314.94.

(3) The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and Sec. 314.50 or Sec. 314.94.

(7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.

This application has not complied with the above regulation.

The Agency filed the NDA over protest, notified the Applicant in writing and reviewed it as filed.

3. Summary of Reviewer Comments on Non-Clinical Sections of NDA 20-996

3.1. CMC Comments

Dermex II Topical Ointment contains 30% (w/w) of the chelated form of 8-Hydroxyquinoline and $ZnCl_2$ in an ointment base. The Applicant considers the active ingredient to be a metal-ligand complex formed by reaction of 1 mole of zinc chloride with 2 moles of 8-hydroxyquinoline (ligand) *in situ* during the manufacture of Dermex II Topical Ointment.

$$ZnCl_2 + 2C_9H_7NO \Rightarrow C_{18}H_{12}N_2O_2Zn + 2HCl$$

Use of 8-hydroxyquinoline as a precipitant for bivalent metal ions is well known. Zinc can form both 1:1 and 1:2 metal ligand complexes with 8-hydroxyquinoline. The 1:2 metal ligand complex (the claimed active ingredient) is both very stable and highly insoluble.

- Without physicochemical analytical data we cannot confirm whether the active ingredient is zinc oxinate (1:2 metal ligand complex), free zinc ions, 8-hydroxyquinoline or a combination of one or more of the stated species.

- No specifications (quality attributes, analytical methods and acceptance criteria) for starting materials, active pharmaceutical ingredient (or drug substance) or proposed finished drug product. Without analytical controls the identity, strength, quality and purity of the drug product cannot be ascertained.

- No stability data submitted in support of the proposed 12 month expiration date.

- No data to evaluate differences in formulations (if any) of the batches used for pivotal clinical studies and the proposed to-be-marketed drug product.

3.2. CMC Micro Comments
The application lacks the following fundamental information needed to assess the microbiological quality of the drug product:

- Statement indicating whether the drug product is sterile or non-sterile.

- Sterilization process validation (if sterile product).

- Microbial limits test methodology and corresponding acceptance criteria, or scientific rationale for lack of microbial limits testing of drug product. (if non-sterile product).

- Validation of preservative effectiveness of preservative system (if any) or demonstration of inherent antimicrobial properties of the non-preserved product.

- Microbiological stability of the drug product.

3.3. Pharmacology/Toxicology Comments
This NDA is considered non-approvable based on the lack of adequate information submitted either:

- to evaluate the safety of Dermex II ointment or

- to bridge to existing data on the individual components of Dermex II ointment.

3.4. Biopharmaceutics/Human Pharmacokinetics Comments

3.5. Biostatistics Comments
Approval is not recommended because:

- The simple case reports of the handful of subjects included in the submission do not meet the criteria of data from "adequate and well-controlled clinical trials." Consequently, there are no data that can be statistically evaluated to support the claims.

4. Clinical Program in Support of NDA 20-996

This NDA has been reviewed with reference to the proposed indications and proposed labeling submitted on 9/15/99. The Applicant has narrowed down the indications in this submission to:

(1) actinic keratosis, (2) basal cell carcinoma and (3) squamous cell carcinoma.

The NDA does not have details of a clinical program to study the proposed indications for Dermex's drug product. The information is given in a one-page "protocol" (See Section 5.2.) used for all indications.

5. Efficacy Evaluation

5.1. Dose-ranging

There were no studies on dose-ranging presented in this NDA for any indication.

5.2. "Protocol" for Clinical Studies for All Indications

One protocol was used for all indications (see Attachment 1). These studies consisted of a blinded phase with application of $ZnCl_2$, 8 hydroxyquinoline or the ointment base, and an open phase when Dermex's zinc oxinate ointment was used.

The Applicant reports that the studies presented in the September, 1999 submission were all conducted in one center by one Investigator in Mexico City, Mexico.

5.3. Indication #1 Actinic Keratosis

One case report form was presented. It is inadequate for data collection to support an NDA. Histology showed squamous cell carcinoma, grade 1. Subsequent biopsy showed "atypical cells" and third biopsy "necrosis".

In the original submission of 3/27/98, there were also 8 single-page case reports on actinic keratosis. They are also inadequate for data collection to support an NDA.

5.4. Indication #2 Basal Cell Carcinoma

Eight case report forms were presented. They are inadequate for data collection to support an NDA (see Attachment 2 for example). Four of the patients continued to show tumor cells even in the last biopsy. In 4 patients, there was no mention of tumor in the last biopsy.

Four sets of photographs were shown, with ulcerated lesions resolving with scarring.

In the original submission of 3/27/98, there were also photographs on 4 cases of basal cell carcinoma, and 14 single-page case reports on this condition. As well, these case reports are inadequate for data collection to support an NDA.

5.5. Indication #3 Squamous Cell Carcinoma

One case report form was presented. It is inadequate for data collection to support an NDA. The patient continued to show tumor cells in the last biopsy.

One set of photographs was shown, with ulcerated lesion resolving with scarring.

In the original submission of 3/27/98, there were also photographs on one case of squamous cell carcinoma.

5.6. Summary Table of Human Data for the Three Proposed Indications

	Case Reports		Photographic Cases	
Indication	Submission '98	Submission '99	Submission '98	Submission '99
AK	10	1	-	-
BCC	14	8	4	
SCC	-	1	1	

AK=actinic keratosis, BCC=basal cell carcinoma, SCC=squamous cell carcinoma

5.7. Additional Non-Human Clinical Data

Descriptions and photographs on veterinary cases of various tumors were also presented both in the original submission of 3/27/98 and the resubmission of 9/15/99. These were not appropriate for the evaluation of safety and efficacy for the proposed indications in human subjects.

5.8. Conclusions on Efficacy

No conclusions can be drawn, as there are no adequate and well controlled studies (see Appendix I for definitions under current regulations) to support efficacy in each of the indications actinic keratosis, basal cell carcinoma and squamous cell carcinoma. The data are not considered adequate (see Appendix I), because of problems in design and in reporting:

1. Besides histologic diagnosis, the enrollment criteria have not been clearly laid out for the studies.
2. Although the protocol indicates initial "blind studies" followed by subsequent open label treatment, the design has not been clearly delineated in terms of the blinding aspects and the use of comparative controls. The zinc oxinate was always applied in the later, open phase. Patient assignment or evaluation for the blind phase has not been reported.
3. The quantity of ointment to be applied, and details of drug administration are not specified or reported.
4. The use of ancillary measures has not been described or reported. These are potentially important in the evaluation, especially in the case of ulcerated lesions.

5. The studies were conducted in one foreign center. Justification for extrapolation to U.S. patients has not been provided. Additionally, in general, single-center trials are not considered adequate to provide substantial evidence for efficacy.
6. There is no documentation that the Investigator for the clinical studies was qualified.

The Applicant claims 100% efficacy for their drug product. This claim cannot be evaluated.

6. Safety Evaluation

6.1. Dataset/Exposure Information
The Applicant states in the "protocol" that over 100 patients had been studied with Dermex's zinc oxinate. However, there was neither any detail on these patients nor information on the number treated per indication.

6.2. Adverse Event Data
No data have been presented to support the Adverse Reactions Section in the Applicant's proposed label:

"The following adverse reactions have been selected on the basis of their potential clinical significance (possible signs & symptoms in parenthesis where appropriate) not necessarily inclusive:

Those indicating need for medical attention where the incidence may be more frequent.

Inflammatory response or allergic reaction; burning feeling at site of application; contact dermatitis (skin rash); increased sensitivity of skin to sunlight; itching; oozing; soreness or tenderness of skin (redness & swelling of normal skin).

Note: A delayed hypersensitivity reaction may occur.

Patch testing for hypersensitivity reaction may be inconclusive.

Those indicating need for medical attention only if they continue to be bothersome.

Darkening of skin; scaling."

The only safety information has been given under the "Conclusion" Section of the "protocol":

> "Dermex II proved to be 100% effective with minimum inflammation. The area treated healed with little or no scarring."

6.3. Dermal Safety and Pharmacokinetic Studies
No dermal safety or pharmacokinetic studies have been presented.

6.4. Demographic, Disease and Drug Interactions
No data on drug-demographic, -disease or -drug interactions are available.

6.5. Conclusions on Safety
No conclusions can be drawn, as there are no adequate and well-controlled studies to support safety in each of the indications. In fact, no safety data have been presented for any of the indications.

7. Summary of Risks and Benefits
No safety data have been presented for evaluation of risks.

There are no adequate and well controlled studies to demonstrate efficacy of Dermex's zinc oxinate in the treatment of actinic keratosis, basal cell carcinoma or squamous cell carcinoma.

Thus, risk/benefit evaluation cannot be performed.

In summary, the Agency has filed this NDA *over* protest, in accordance to 21 CFR 314.101(a)(3), and reviewed it as filed. Review of the Clinical Section of this NDA confirms that there are no adequate and well studies to support the safety or efficacy in the treatment of the three indications actinic keratosis, basal cell carcinoma and squamous cell carcinoma. Therefore, approval of this NDA is not recommended.

8. Question for Discussion
The Agency plans to issue a Non-Approvable action on NDA 20-996. Does the Committee have any comments?